Journal of Neuromuscular Diseases 2 (2015) 63–72
DOI 10.3233/JND-140053
IOS Press

Research Report

Compliance to Care Guidelines for Duchenne Muscular Dystrophy

Erik Landfeldt[a,b], Peter Lindgren[c], Christopher F. Bell[d], Claude Schmitt[e], Michela Guglieri[f], Volker Straub[f], Hanns Lochmüller[f,1] and Katharine Bushby[f,*,1]
[a]*OptumInsight, Stockholm, Sweden*
[b]*Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden*
[c]*Medical Management Centre, Department of Learning, Informatics, Management and Ethics, Karolinska Institutet, Stockholm, Sweden*
[d]*GlaxoSmithKline, Research Triangle Park, North Carolina, USA*
[e]*GlaxoSmithKline, Brentford, Middlesex, UK*
[f]*Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK*

Abstract.
Background: International care guidelines for Duchenne muscular dystrophy (DMD) were published in 2010, but compliance in clinical practice is unknown.
Objective: The objective of our study was to compare real-world DMD care in Germany, Italy, the UK, and the US with the clinical recommendations.
Methods: DMD patients from Germany, Italy, the UK, and the US were identified through Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases (TREAT-NMD) registries and invited with a caregiver to complete a questionnaire with questions regarding DMD-related healthcare. Estimates of care were stratified by disease stage (early/late ambulatory/non-ambulatory) and compared against the care guidelines.
Results: A total of 770 patients (173 German, 122 Italian, 191 UK, and 284 US) completed the questionnaire. Poor compliance to guidelines of routine follow-up by neuromuscular, cardiac, and respiratory specialists, physiotherapy, and access to medical devices and aids were observed in all countries. Less than 27% (209 of 770) of patients met all absolute recommendations, ranging from 9% (11 of 122) in Italy to 37% (70 of 191) in the UK, and from 49% (76 of 155) in the early ambulatory class to 16% (33 of 205) in the late non-ambulatory class.
Conclusions: We show that the medical management of DMD varies substantially between Germany, Italy, the UK, and the US. Experience of real-world DMD care appears to be in poor agreement with the DMD clinical guidelines and increased compliance is urgently needed to improve treatment outcomes and enable patients to lead fulfilling, independent lives into adulthood.

Keywords: Muscular dystrophy, duchenne, practice guideline, delivery of health care, observational study

INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular disease with an incidence of about one in 3800–6300 live male births [1]. The fatal condition is characterized by progressive muscle degeneration caused by a dystrophin mutation. Affected children become non-ambulatory usually in their early teens and experience serious respiratory, orthopaedic, and cardiac complications due to the aggressive disease progression. Untreated, the mean age at death is 19 years [2], but the introduction of glucocorticoid therapy, proactive cardiac management, and nocturnal ventilatory support has prolonged life

[1]Equal contribution.

*Correspondence to: Professor Katharine Bushby, Institute of Genetic Medicine, International Centre for Life, Central Parkway, Newcastle upon Tyne, NE1 3BZ, UK. Tel.: +44 191 241 8757; E-mail: kate.bushby@ncl.ac.uk.

ISSN 2214-3599/15/$35.00

expectancy into the third and sometimes fourth decade of life.

To extend the best available practice in management as widely as possible, comprehensive clinical care guidelines for DMD were published in 2010 [3, 4]. The DMD care guidelines were generated by an international, multidisciplinary group of experts utilising methodology under the guidance of the United States of America (US) Centers for Disease Control and Prevention, and have achieved National Institute for Health and Care Excellence process accreditation in the United Kingdom (UK). An extensive dissemination programme was also launched, including a family guide translated into around 30 languages [5].

Despite global promulgation, it is not known to what extent the DMD care guidelines are followed in clinical practice. The objective of the current study was to compare the real-world patient/family reported experience of DMD medical management in Germany, Italy, the UK, and the US with the clinical guidelines. Our aim was to identify aspects of care in need of further harmonisation and where the current standards are not being met.

MATERIALS AND METHODS

Summary of DMD clinical care guidelines

The DMD care guidelines encompass a set of integrated treatment recommendations for both preventive and active interventions to address the primary and secondary manifestations and complications throughout the disease progression. In brief, optimum disease management involves co-ordination of care with prescribed periodicity in visits to neuromuscular, cardiac, and respiratory specialists, regular physiotherapy, and staged assessments and interventions for cardiac and respiratory function (Table 1). Initiation of glucocorticoid therapy should be considered for patients between four to six years of age, when motor function reaches a plateau. Indications for glucocorticoids in non-ambulatory patients are more relative than absolute due to insufficient efficacy and safety evidence. Daily and intermittent dosing are commonly prescribed glucocorticoid regimens.

As an effect of the disease progression, patients with DMD depend on medical aids and devices to manage the loss in muscle strength, maintain independence and function as much as possible, and carry out activities of daily living. These include at different times ankle-foot orthoses (AFOs) for contracture control, wrist-hand orthoses (WHOs) for patients with tight long finger flexors, knee-ankle-foot orthosis (KAFO), knee orthosis (KO), and standing devices. Recommendations for wheelchairs include access to manual wheelchairs for late ambulatory patients and power wheelchair for non-ambulatory patients.

Participants and procedures

DMD patients and one of their caregivers (e.g., a parent) were identified through the Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases (TREAT-NMD) national registries in Germany, Italy, the UK, and the US. All four DMD registries have been in operation for at least seven years ensuring good representation across age groups. To be eligible, patients were required to fulfil the following criteria: (i) Male, (ii) DMD diagnosis, and (iii) Age $\geq$5 years.

Eligible patient-caregiver pairs were invited to complete a questionnaire online containing questions regarding the patient, his health status, and DMD-related visits to physicians and other healthcare professionals, clinical tests and assessments, medication use, as well as access to medical aids and devices. Recall periods were specified depending on the frequency of resource use in clinical practice and care guidelines (one month, six months, or one year). Study materials were presented in the native language of each country and subject to review by the TREAT-NMD coordination team to ensure understandability, accuracy, and completeness. A pilot study was conducted to further establish questionnaire validity. Additional study details have been previously published [6].

All participants provided informed consent. Study ethical approval was granted from Ludwig-Maximilians- Universität München (Germany), Comitato Etico IRCCS E. Medea - Associazione La Nostra Famiglia (Italy), North East Research Ethics Service, NHS (UK), and the Western Institutional Review Board (US). Approval was also obtained from the TREAT-NMD Global Databases Oversight Committee.

Statistical analysis

We assessed the number of visits to physicians and other healthcare professionals, stratified by type of practitioner as listed in the DMD care guidelines summarized in Table 1 (i.e., neuromuscular specialists, cardiac specialists, respiratory specialists, orthopaedists, physiotherapists, therapists and psychologists, and speech and language therapists) during

Table 1
Summary of DMD care guidelines [3, 4]

Care component	Frequency (minimum)	Practitioner	Aims
Neuromuscular management	Every six months	Neuromuscular specialist	Evaluation of disease status and progression (muscle strength, function, and range of movements); anticipatory planning of future developments and prevention of complications (e.g., scoliosis); ensuring immunisations schedule (e.g., varicella zoster, pneumococcal vaccine, and flu jab); planning treatment interventions (e.g., glucocorticoid therapy), efficacy and side-effect management of pharmacological treatments; evaluation of psychological issues, daily activity, and functioning
Cardiac management	At diagnosis, annually in ambulatory patients and every six months in non-ambulatory patients	Cardiac specialist	ECG and echocardiogram to evaluate dyskinesia, LV dysfunction and dilated cardiomyopathy; prompt initiation of treatment (ACE-inhibitors and/or beta blockers) with early signs of cardiac dysfunction
Respiratory management	Annually in ambulatory patients and every six months in non-ambulatory patients	Respiratory specialist	Evaluation of respiratory function (e.g., FVC and cough peak) to allow timely prevention and management of complications; ensuring immunisation schedule (e.g., pneumococcal vaccine and flu jab); trigger further respiratory investigations (e.g., overnight pulse oximetry and haemogas analysis); trigger respiratory interventions (e.g., respiratory physiotherapy, cough assist machine, NIV, and tracheostomy)
Orthopaedic management	As indicated	Orthopaedist	Evaluation of surgical options for joint contractures (e.g., Achilles tendons and hips); monitoring for scoliosis and interventions (e.g., spinal fusion)
Physiotherapy	Every six months	Physiotherapist	Assessment of disease progression and complications (e.g., joint contractures and spinal deformities); trigger interventions for management of complications (e.g., orthoses and referral to orthopaedic surgeon); advice about stretching exercises (to be done locally 4–6 times per week by parents or local physiotherapist at home or at school) and monitoring of progresses
Psychosocial therapy	As indicated	Therapist and/or psychologist	Provision of family support; early evaluation and timely interventions for speech development, learning, and behavioural issues; evaluation of coping strategies; promoting independency and social development
Speech and language therapy	As indicated	Speech and language therapist	Evaluation of speech developmental delay and establishment of prompt interventions; assessment of dysphagia

ECG = Electrocardiography. LV = Left ventricle. FVC = Forced vital capacity. NIV = Non-invasive ventilation. AFO = Ankle-foot orthosis. KAFOs = Knee-ankle-foot orthosis.

the last six months. In addition, we estimated visits to general practitioners (GPs) and paediatricians during the last six months as these practitioners may provide supportive neuromuscular care in some settings. We also assessed pulmonary evaluations (FVC and peak cough flow) during the last six months, current glucocorticoid therapy, as well as current access (however provided, e.g., by a clinic/hospital or through a self-made purchase) to AFOs, KAFOs, KOs, WHOs, standing devices, and wheelchairs.

We related our results to the progression of DMD by classifying patients into four groups defined in terms of current ambulatory status and age: (i) early ambulatory (approx. age 5 to 7 years), (ii) late ambulatory (approx. age 8 to 11 years), (iii) early non-ambulatory (approx. age 12 to 15 years), and (iv) late non-ambulatory

(approx. 16 years of age, or older). Study results were compared with the DMD guidelines (Table 1).

We compared demographic characteristics and healthcare resource use between countries and ambulatory classes using Kruskal-Wallis and χ^2 tests. We considered p-values <0.05 to be significant. All analyses were conducted in Stata 11 (StataCorp LP, Collage Station, TX, US).

RESULTS

A total of 770 patient-caregiver pairs satisfied all study criteria and completed the questionnaire between July, 2012, and July, 2013 (42% overall response rate). Patients had a mean age of 14 years (range 5–43) and a median age of 12 years (IQR 9–17) (Table 2).

DMD care exhibited notable heterogeneity with respect to visits to physicians and other healthcare professionals, both across stages of disease progression ($p < 0.001$) and the studied countries ($p < 0.001$) (Fig. 1). Suboptimal compliance to guidelines of follow-up by neuromuscular, cardiac, and respiratory specialists was noted across all strata. The proportion of German, Italian, UK, and US patients that reported visiting a GP or paediatrician during the last six months was estimated at 66% (115 of 173), 34% (42 of 122), 62% (119 of 191), and 60% (171 of 284), respectively. Moreover, regardless of the increased importance of routine follow-up due to side effects, less than 27% (21 of 78) of Italian patients taking glucocorticoids had visited a neuromuscular specialist during the last six months, compared with 72% (56 of 78) from Germany, 68% (81 of 120) from the UK, and 62% (131 of 210) from the US.

The pattern of physiotherapy (recommended minimum follow-up once every six months) was significantly different between the studied countries and ambulatory classes, both with respect to the mean absolute number of visits ($p < 0.001$) and proportion of patients with any visit ($p < 0.001$) (Fig. 1). In patients with scoliosis, approximately 80% (62 of 78) of the German sample, 50% (25 of 50) of the Italian sample, 55% (29 of 53) of the UK sample, and 48% (38 of 80) of the US sample had visited a physiotherapist during the last six months, regardless of the increased need to manage current and alleviate future complications. The proportion of patients with scoliosis that had visited an orthopaedist during the last six months were 37% (29 of 78) of the German sample, 18% (9 of 50) of the Italian sample, 23% (12 of 53) of the UK sample, and 29% (23 of 80) of the US sample.

The guidelines recommend pulmonary evaluations, including FVC and peak cough flow, once every six months at a minimum for non-ambulatory patients. The proportion of German, Italian, UK, and US patients meeting this criterion was 81% (76 of 94), 66% (37 of 56), 61% (51 of 83), and 62% (78 of 126), respectively. The corresponding proportions for patients receiving ventilatory support was 62% (16 of 26), 46% (11 of 24), 43% (15 of 35), and 66% (27 of 41).

Despite standardized guidance, the proportion of patients currently taking glucocorticoids (shown above each column in Fig. 2) varied significantly between countries and ambulatory classes and there were

Table 2
Demographic characteristics of the study participants ($n = 770$ patients)

	Germany	Italy	The UK	The US	p-value
n	173 (100%)	122 (100%)	191 (100%)	284 (100%)	N/A
Age, years	13 (9–17)	12 (8–17)	12 (8–17)	12 (9–17)	0.547
Ambulatory class					
Early ambulatory (age 5 to 7 years)[a]	30 (17%)	31 (25%)	46 (24%)	48 (17%)	0.084
Late ambulatory (age 8 to 11 years)[a]	49 (28%)	35 (29%)	62 (32%)	110 (39%)	0.074
Early non-ambulatory (age 12 to 15 years)[b]	47 (27%)	24 (20%)	34 (18%)	49 (17%)	0.058
Late non-ambulatory (16 years of age, or older)[b]	47 (27%)	32 (26%)	49 (26%)	77 (27%)	0.983
Ventilation support	26 (15%)	24 (20%)	35 (18%)	41 (14%)	0.474
Comorbidities and concurrent diagnoses					
Attention-deficit hyperactivity disorder (ADHD)	12 (7%)	8 (7%)	5 (3%)	54 (19%)	<0.001
Autism spectrum disorder (ASD)	5 (3%)	1 (1%)	13 (7%)	22 (8%)	0.011
Cardiomyopathy	47 (27%)	17 (14%)	49 (26%)	60 (21%)	0.034
Depression	5 (3%)	3 (2%)	6 (3%)	32 (11%)	<0.001
Dysphagia	12 (7%)	7 (6%)	20 (10%)	22 (8%)	0.433
Obsessive-compulsive disorder (OCD)	4 (2%)	2 (2%)	9 (5%)	38 (13%)	<0.001
Scoliosis	78 (45%)	50 (41%)	53 (28%)	80 (28%)	<0.001

Note: Data presented as *n* (%) or median (IQR) unless otherwise stated. Because of rounding, percentages might not add up to 100% exactly. N/A = Not applicable. [a]An ambulant patient older than the specified age intervals was included in the late ambulatory patient group.[b]A non-ambulant patient younger than the specified age intervals was included in the early non-ambulatory patient group.

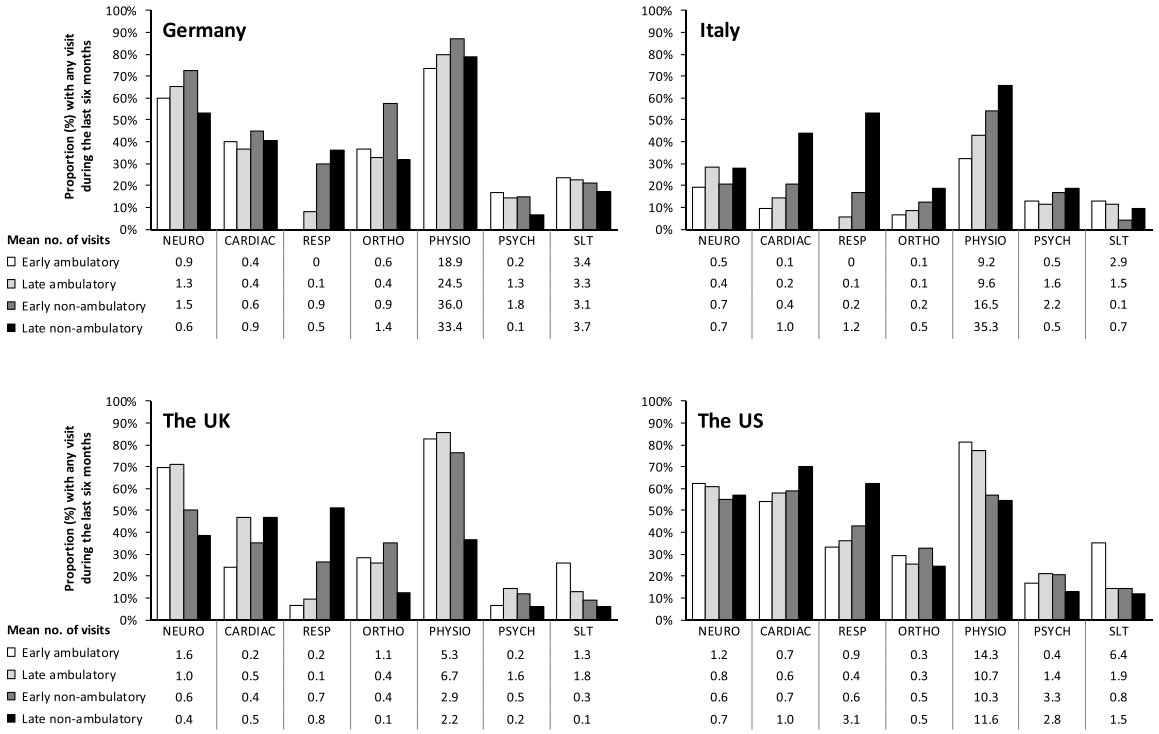

Fig. 1. Visits to physicians and other healthcare professionals during the last six months. NEURO = Neuromuscular specialist. CARDIAC = Cardiac specialist. RESP = Respiratory specialist. ORTHO = Orthopaedist. PHYSIO = Physiotherapist. PSYCH = Therapist and/or psychologist. SLT = Speech and language therapist.

also large differences with respect to glucocorticoid medications and regimens prescribed ($p < 0.003$ for comparison across countries and ambulatory classes). Deflazacort (not approved by the US Food and Drug Administration, FDA) was the most commonly used glucocorticoid in the German, Italian, and US sample, whereas most UK patients were prescribed prednisolone (Fig. 2A). Daily dosing dominated the prescription pattern in the US sample, whereas German and UK patients also were prescribed intermittent regimens, and Italian patients alternate day regimens (Fig. 2B). High-dose weekend regimens were exclusively seen in US patients.

The proportion of German patients with access to any orthosis (AFO, KAFO, KO, and/or WHO) was estimated at 29% (50 of 173). The corresponding proportions for the Italian, UK, and US sample were 65% (79 of 122), 65% (125 of 191), and 70% (199 of 284), respectively. Access to standing devices, estimated at 12% (93 of 770) with minor deviations between countries, ranged from 0% (0 of 155) in the early ambulatory stratum, to 6% (15 of 256), 32% (50 of 154), and 14% (28 of 205) in the late ambulatory, early non-ambulatory, and late non-ambulatory class. Among late ambulatory patients, 55% (27 of 49) of the German sample had access to wheelchairs. The corresponding proportions for the Italian, UK, and US sample were 26% (9 of 35), 76% (47 of 62), and 58% (64 of 110), respectively. Approximately 88% (315 of 359) of all non-ambulatory patients reported having access to a power wheelchair.

Table 3 presents a summary of our findings of compliance to the absolute recommendations in the DMD care guidelines. In the pooled sample, the proportion of patients meeting all absolute recommendations was 49% (76 of 155), 30% (76 of 256), 16% (24 of 154), and 16% (33 of 205) in the early ambulatory, late ambulatory, early non-ambulatory, and late non-ambulatory class, respectively.

DISCUSSION

This study has demonstrated that the real-world experience of the medical management of DMD in four countries falls short in many areas of the standards set out in the internationally generated care considerations. Poor compliance to guidelines of routine

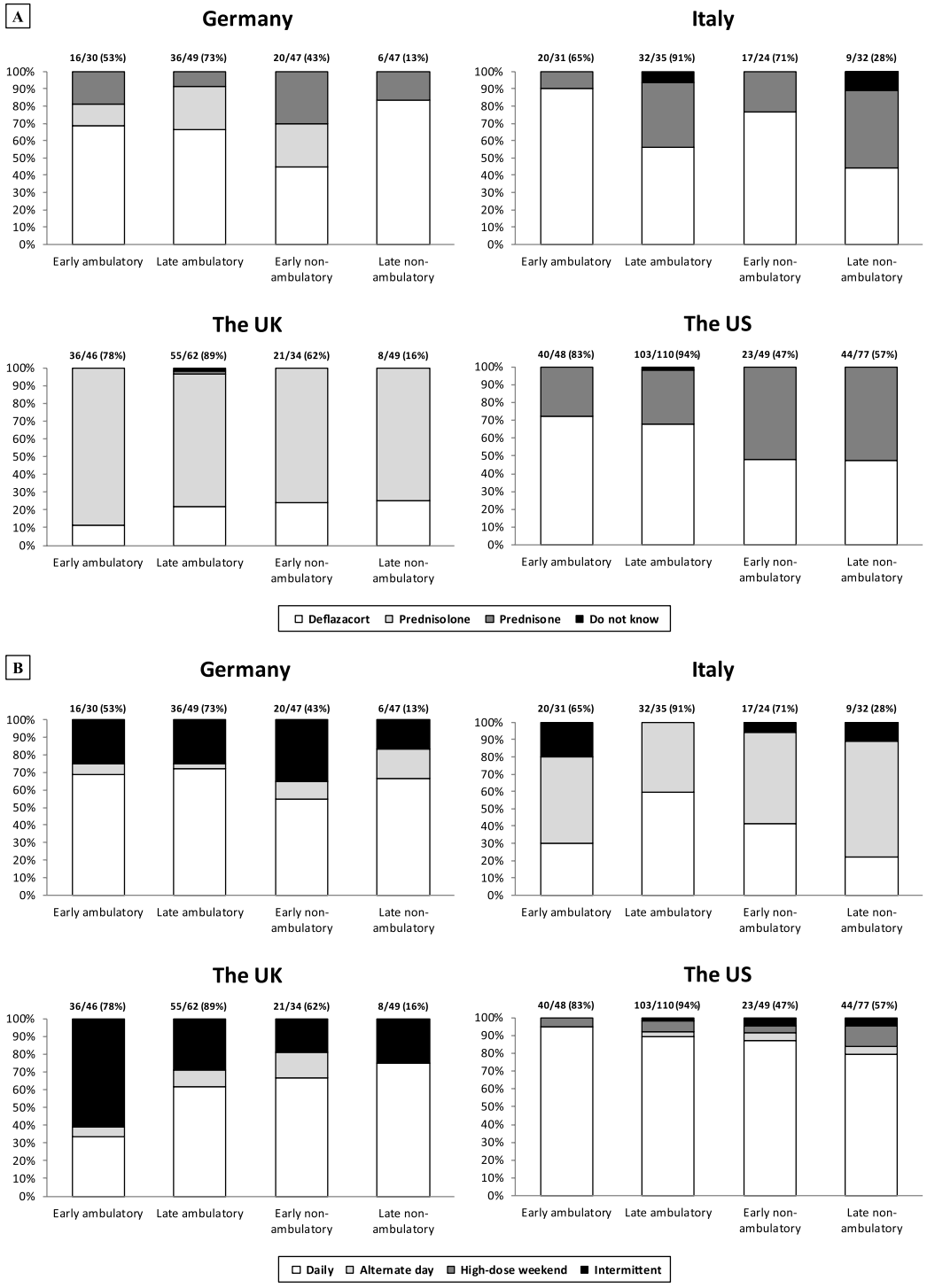

Fig. 2. Current use of glucocorticoid medications (panel A) and regimens (panel B). Note: The figures above each column represent the proportion of patients in each stratum that were currently taking glucocorticoids. Alternate day: for example every other day. High-dose weekend: a high dose taken for example on Fridays and Saturdays. Intermittent: for example 10 days on, 10 days off.

Table 3
Summary of compliance to absolute care recommendations

Care component	Proportion of patients meeting guideline recommendation			
	Germany	Italy	The UK	The US
Neuromuscular management[a]	63% (58%–70%)	25% (17%–32%)	59% (52%–66%)	59% (53%–65%)
Cardiac management[b]	43% (32%–53%)	34% (21%–47%)	42% (31%–53%)	66% (57%–74%)
Respiratory management[b]	33% (23%–43%)	38% (24%–51%)	41% (30%–52%)	55% (46%–64%)
Physiotherapy[c]	80% (74%–86%)	48% (39%–57%)	71% (64%–77%)	68% (63%–74%)
Access the medical devices and aids[d]	79% (73%–85%)	62% (54%–71%)	88% (84%–93%)	75% (70%–80%)
All components[e]	25% (18%–31%)	9% (4%–14%)	37% (30%–44%)	30% (25%–35%)

Note: Data presented as proportion % (95% CI). [a]Minimum of one specialist visit during the last six months. [b]Minimum of one specialist visit during the last six months for non-ambulatory patients. [c]Minimum of one physiotherapy session during the last six months. [d]Manual wheelchair access for late ambulatory patients and power wheelchair access for non-ambulatory patients. [e]Perfect compliance to annual follow-up by cardiac and respiratory specialist assumed for ambulatory patients.

follow-up by neuromuscular, cardiac, and respiratory specialists, physiotherapy, and access to medical devices and aids were observed in all countries, and we also noted remarkable heterogeneity between countries in visits to orthopaedists, therapists and psychologists, and speech and language therapists, as well as glucocorticoid therapy. Our results describe the experience of the process of delivery of care and cannot be directly extrapolated into clinical or patient-related outcomes. However, given the clear correlation previously demonstrated between glucocorticoid therapy, proactive cardiac and pulmonary management, ventilation support, and increased survival, the substantial variation and lack of access to these interventions demonstrated in some areas is of concern.

The DMD clinical care guidelines emphasize the pivotal role of regular visits to a neuromuscular specialist to deliver patient centric care. Contrary to these recommendations, our results show that far from all patients are seen by any doctor (GP or specialist) every six months, irrespectively of disease stage and current exposure to glucocorticoids. We also identified remarkable differences in the frequency of physiotherapy between countries and ambulatory classes, where for example German patients had on average nine times as many visits to physiotherapists as their UK counterparts. Additional research is needed to understand the effect of these discrepancies on clinical outcomes and patient satisfaction.

We found respiratory management, including frequency of follow-up by respiratory specialists and pulmonary evaluations such as FVC and peak cough flow, to be in poor compliance with recommended thresholds. Our results displayed the expected pattern of increased care in advanced disease stages, and for patients requiring ventilation support, but the intensity of care in absolute numbers was strikingly low. Our data also show that the majority of pulmonary evaluations in early disease stages are made by practitioners other than respiratory specialists. Poor compliance to guidelines was also found for cardiac management of non-ambulatory patients, where less than half (177 of 359) reported visiting a cardiac specialist during the last six months. It is evident that additional measures must be taken to decrease variability and increase alignment with guidelines of cardiac and respiratory management to reduce morbidity and improve survival in DMD.

As underscored in the guidelines, the medical care of patients with DMD is not complete in the absence of psychosocial treatment and support to cope with the aggressive disease progression and manage potential mental and behavioural disorders. In our sample, less than 15% (110 of 770) of patients had visited a psychologist or therapist during the last six months. Increased effort must be made to further integrate psychosocial management in the treatment strategy of DMD to help maintain patient quality of life throughout the disease progression. Data from this study also highlight surprising differences between countries with respect to the prevalence of diagnosis for mental and behavioural disorders, in particular concerning the US where 51% (146 of 284) of patients had diagnosis for ADHD, ASD, depression, and/or OCD compared with 15% (26 of 173), 11% (14 of 122), and 17% (33 of 191) of German, Italian, and UK patients. Reasons for this heterogeneity could be associated with inter-country differences in the use of diagnosis codes in clinical practice and the general provision and structure of healthcare, but cannot be elicited from this study.

Although the efficacy of glucocorticoids in DMD is well-demonstrated, treatment recommendations are limited by lack of data on comparative efficacy of alternative regimens, as well as results of long-term exposure in different treatment groups. For these reasons, it is difficult to assess compliance to guidelines in

our sample. Nonetheless, we confirmed that there are substantial differences between countries with respect to the proportion of patients treated with glucocorticoids in the four ambulatory classes. We also observed considerable variability in the prescription patterns of the three existing drugs, as well as regimens. These findings are in agreement with recent data published by Griggs et al. [7], who also found notable variability in the glucocorticoid treatment patterns between countries. The mechanisms behind these diverse prescribing behaviours warrant additional research and further standardization of glucocorticoid therapy is urgently needed to improve treatment outcomes and overall DMD care. Studies, such as the ongoing FOR-DMD trial [8], are also crucial to further understand the benefits and risks of different glucocorticoid regimens in DMD. In the US, the most common glucocorticoid was deflazacort, which is currently not approved by the FDA. Anecdotal evidence from US patients and physicians suggests that use of deflazacort in DMD relies on accessing the drug from other countries. Efforts to achieve approval for deflazacort from the FDA are being addressed by the FOR-DMD investigators and others pending the results of that study.

Orthoses help maintain functional ability and muscle extensibility, and prevent or minimise contractures, and adequate access to such aids is thus an important aspect of DMD care. Surprisingly, in the German sample, only 29% (50 of 173) of patients reported having access to any orthosis, compared with 65% (79 of 122), 65% (125 of 191), and 70% (199 of 284) in the Italian, UK, and US sample, respectively. The lower access in Germany may be associated with the relatively higher intensity of physiotherapy, but requires further investigation. We also noted large differences between countries with respect to wheelchair access in the late ambulatory disease stage, a situation which must be addressed to enhance the possibility for patients to participate in society for as long as possible.

We identified three previous studies [9–11] examining different aspects of self-reported real-world DMD care in various settings. The first study [9] investigated cardiac management in 30 Canadian DMD patients and showed suboptimal frequency in visits to cardiac specialists, including poor compliance by patients to attend new appointments. The second study [10] investigated palliative care of 34 US DMD patients. This study demonstrated low utilization of common healthcare services in DMD palliative care and conclude that awareness of related services must be improved. The third study [11] reported aspects of general healthcare, including palliative care, in 34 US patients with DMD or Becker muscular dystrophy, and conclude that healthcare utilization is suboptimal. It is challenging to directly compare our estimates with previous findings because they in most cases only describe the type of healthcare that were utilized (not frequency of care) and since they do not stratify results by disease stage. Still, our conclusions are consistent with findings from previous work.

Potential reasons for the observed heterogeneity in compliance to the DMD care guidelines may be related to differences in the delivery of and access to care in general, and the availability of specialized neuromuscular clinics in particular. We know that in the UK, almost all paediatric and around 70% of adult patients attend a neuromuscular centre, with similar estimates reported for adult German patients [12]. Care provided in specialized clinics would be expected to encompass both the expertise and resources needed to deliver multidisciplinary, coordinated, patient-centric care in accordance with the clinical care guidelines. As a consequence, specialized centres should directly enhance compliance to care guidelines. Specialized centres may also contribute to increased patient and family satisfaction with healthcare in general through increased clinical attention, regular follow-ups, timely information regarding best care practices, available treatment options, etc. [12]. This, in turn, may improve compliance indirectly through increased patient-family motivation and willingness to participate in the DMD care (e.g., attending all scheduled visits, perform stretching exercises at home as instructed, and adhering to prescribed regimens). However, in many countries, including the UK and Germany, far from all specialized clinics have access to all necessary expertise internally and instead rely on referrals to local providers for some core care services [13]. As a result, DMD care is seldom provided exclusively at a single centre, but rather divided between multiple access points which may result in both suboptimal access to and utilization of care services. Consequently, given the poor compliance observed in our study, further improvements to the organization, coordination, and delivery of DMD care, as well as the transition from paediatric to adult care, is needed to increase compliance to care recommendations and harmonize the medical management of DMD internationally. In addition, other characteristics of national healthcare systems, for example government funded programs versus private insurance schemes and the degree of cost sharing for services, are also likely to impact on both the provision of healthcare (e.g., supply of specialized services), as well as the possibilities and willingness for patients to

utilize healthcare services. The suboptimal utilization of physiotherapy in adult DMD UK patients, for example, could be related to the fact that such healthcare services are typically not funded through the National Health Service, and although services may be available privately, few patients choose, or can afford, to utilize them. Further research into these aspects of access to care is essential to help understand how to improve compliance to DMD guidelines and ultimately improve care outcomes. Lastly, given that the care guidelines were published in 2010, and our study conducted in 2012/2013, additional time may be needed to allow for alignment of care in some countries and regions, which could result in increased compliance in the future.

We appreciate that there are limitations of our study due to its cross-sectional design and the self-reported nature of the data. Patient-caregiver pairs indicated DMD-related healthcare use for various recall periods in a single questionnaire administration, and our findings may consequently be subject to recall bias. To minimize this potential issue, recall periods were carefully chosen in agreement with the clinical care guidelines and we amended our data collection protocols following a pilot study which was carried out to further increase the validity of study replies. Still, given the intensity of DMD care, some patient-caregiver pairs may have overlooked some healthcare consultations, which may have led to an underestimation of the frequency of care in absolute numbers reported in this study, but not bias relative differences between countries and ambulatory classes. In addition, there are two possible sources of bias which we cannot assess. First, our sample may have been subject to selection bias as caregivers that are particularly involved in the care of their child may also be more interested and motivated to be involved in research and complete our survey, resulting in an overestimation of the overall experience of care. On the other hand, of those listed in the TREAT-NMD network registries, patient-caregiver pairs that were particularly dissatisfied with the DMD care received could possibly also have been more motivated to take part in our study (to voice their complaints). We are unable to comment further on the implications of these biases but believe that overall our study is likely to be a representative snapshot of the experienced care in the countries studied.

We have shown that the medical management of DMD varies substantially between Germany, Italy, the UK, and the US, a finding which needs additional investigation. Experience of real-world DMD care appears to be in poor agreement with the DMD clinical guidelines, and further standardisation and increased compliance is urgently needed to improve treatment outcomes and enable patients to lead fulfilling, independent lives into adulthood.

ACKNOWLEDGMENTS

This study was sponsored by GlaxoSmithKline (study number HO-11-794).

The authors gratefully acknowledge Maggie C. Walter, MD, MA, Simone Thiele, and Olivia Schreiber, MD (Friedrich-Baur-Institute, Dept. of Neurology, Ludwig-Maximilians-University, Munich, Germany), Filippo Buccella, Pharm. D, Fernanda G. De Angelis, PhD, Francesca Ceradini, PhD, and Andrea Negroni, ICT Solution Architect (Registro Pazienti DMD/BMD Italia - Parent Project Onlus), Angela Stringer (DMD Registry, Action Duchenne), Emma Heslop, MSc (TREAT-NMD), and Holly L. Peay, MS, CGC, and Ann S. Martin, MS, CGC (DuchenneConnect) for their contribution to the set-up of the study and patient recruitment.

We acknowledge support for TREAT-NMD from the European Commission through FP6 (contract number 036825) and the Second Public Health Programme (contract number 2012 3307), as well as support from the AFM (contract number 16104). The German DMD registry acknowledges additional support from the German Duchenne Parent Project „aktion benni &co“ (www.benniundco.eu), and the Deutsche Gesellschaft für Muskelkranke (DGM) e.V. (www.dgm.org). The UK DMD Registry acknowledges support and funding from Action Duchenne, a patient led charity. The DuchenneConnect Registry acknowledges support and funding from Parent Project Muscular Dystrophy (PPMD), the largest non-profit organization in the United States focused on finding a cure for Duchenne.

CONFLICT OF INTEREST

Mr. Landfeldt is a consultant to GlaxoSmithKline through his employment at OptumInsight but was not compensated for his contributions as an author on this manuscript. Dr. Lindgren has acted as a consultant to GlaxoSmithKline. Mr. Bell and Mr. Schmitt are employees and shareholders of GlaxoSmithKline. Dr. Guglieri, Dr. Straub, Dr. Lochmüller, and Dr. Bushby report no conflict of interest.

CONTRIBUTIONS

Mr. Landfeldt, Dr. Lindgren, and Mr. Bell designed the study with input from Dr. Lochmüller and Dr.

Bushby. Mr. Landfeldt, Dr. Lochmüller, and Dr. Bushby designed the study questionnaire with input from the other authors. Mr. Landfeldt co-ordinated ethics approval processes and managed the collection of data. Mr. Landfeldt designed, implemented, and executed the statistical analysis. Mr. Landfeldt, Dr. Lochmüller and Dr. Bushby led the interpretation of findings with input from the other authors. Mr. Landfeldt drafted the manuscript. All authors reviewed the manuscript and approved the decision to submit for publication.

REFERENCES

[1] Mendell, J. R., Shilling, C., Leslie, N. D., et al. Evidence-based path to newborn screening for Duchenne muscular dystrophy. Ann Neurol. 2012; 71: 304-313.

[2] Eagle, M., Bourke, J., Bullock. R., et al. Managing Duchenne muscular dystrophy–the additive effect of spinal surgery and home nocturnal ventilation in improving survival. Neuromuscul Disord 2007; 17: 470-475.

[3] Bushby, K., Finkel, R., Birnkrant, D. J., et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: Diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2010; 9: 77-93.

[4] Bushby, K., Finkel, R., Birnkrant, D. J., et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: Implementation of multidisciplinary care. Lancet Neurol 2010; 9: 177-189.

[5] TREAT-NMD Neuromuscular Network. Available from: http://www.treat-nmd.eu

[6] Landfeldt, E., Lindgren, P., Bell. C., et al. The Burden of Duchenne Muscular Dystrophy: An International, Cross-Sectional Study. Neurology 2014; 83: 529-536.

[7] Griggs, R. C., Herr, B. E., Reha, A., et al. Corticosteroids in Duchenne muscular dystrophy: Major variations in practice. Muscle Nerve 2013; 48: 27-31.

[8] Hoffman, E. P., Reeves, E., Damsker, J., et al. Novel approaches to corticosteroid treatment in Duchenne muscular dystrophy. Phys Med Rehabil Clin N Am 2012; 23: 821-828.

[9] O'Brien, L., Varadi, R., Goldstein, R. S., Evans, R. A. Cardiac management of ventilator-assisted individuals with duchenne muscular dystrophy. Chron Respir Dis 2014; 11: 103-110.

[10] Arias, R., Andrews, J., Pandya, S., et al. Palliative care services in families of males with Duchenne muscular dystrophy. Muscle Nerve 2011; 44: 93-101.

[11] Andrews, J. G., Davis, M. F., and Meaney, F. J. Correlates of care for young men with Duchenne and Becker muscular dystrophy. Muscle Nerve 2014; 49: 21-25.

[12] Personal communication Sunil Rodger, Newcastle University (October, 2014).

[13] Rodger, S., Lochmüller, H., Tassoni, A., et al. The TREAT-NMD care and trial site registry: An online registry to facilitate clinical research for neuromuscular diseases. Orphanet J Rare Dis 2013; 8: 171.